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EDITORIAL COMMENT

On the Fledgling Field of Mechanical Circulatory Support*

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The First Flights

When the Wright brothers launched the *Kitty Hawk*, no one ran alongside to test whether the machine would win over man for the first journey. The news was that the machine could fly. Early experiences demonstrated the superiority of mechanical devices, including the device used in this trial, to inotropic therapy for "bridging" transplant candidates until donor hearts became available. The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial demonstrated that mechanical support could extend life in patients who were not transplant candidates, with a survival of 52% at 1 year (1). Overall survival at 2 years was 29% at the final analysis and 38% during the last half of the REMATCH trial (2).

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The INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial (3) in this issue of the *Journal* reports the next fledgling flight for durable mechanical circulatory support. The nonrandomized trial design reflects the ambivalence in the developing field; the dismal outcome of failed medical therapy precludes ethical randomization but is not well enough established as a regulatory landmark for devices to pass. Even without a comparable control group, this trial does effectively close the question about this device in this population. A relative risk reduction of 50% is statistically significant, but the absolute mortality of 75% at 1 year is not an acceptable outcome for a device intended for durable support.

Who Needs Wings?

Recent progress in mechanical circulatory support has been held back by inadequate identification of the patients who are heading toward early death but are not yet dying. Finding appropriate patients for ventricular assist devices (VADs) should be somewhat easier than for cardiac transplantation, for which patient selection involves not only the severity and irreversibility of heart failure, but also the gamble of uncertain waiting times for donor hearts. For both of these decisions, however, the term "end-stage" has been too imprecise. The INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support) study has delineated clinical profiles of advanced heart failure (Table 1) that are becoming more objective as these data accumulate.

The REMATCH trial was designed to focus primarily on ambulatory nontransplant candidates in profiles 4 and 5, but those actually consenting were more severely ill. Most REMATCH patients were on inotropic infusions and in profiles 2 or 3 (1). By design, the patients in the INTrEPID trial were also in profiles 2 and 3. These populations on intravenous inotropic therapy who received VADs in these 2 trials were equivalent in terms of the robust predictors of advanced heart failure outcome: average baseline sodium 134 mEq/l, creatinine 1.8 mg/dl, and pulmonary wedge pressure 25 mm Hg (4). The mean age was 60 years in the present INTrEPID trial compared with 67 in the REMATCH trial, in which younger patients fared better. With devices, the 1-year survival for patients on baseline inotropic therapy was 49% from the REMATCH trial, compared with only 27% in the present trial.

The patients not receiving VADs in the present trial appeared more compromised than the VAD group, with serum sodium of 128 mEq/l, creatinine of 2.1 mg/dl, and pulmonary capillary wedge pressure of 29 mm Hg. It is not surprising that these patients had a survival without devices that was worse than the comparable REMATCH patients, 11% versus 24%. Further differences between the device and medical group in the present trial were 8% versus 28% women and 32% versus 56% prior bypass surgery. These differences, as well as the financial reimbursement status, may also have influenced the selection for devices. The medical therapy group in the INTrEPID trial is thus not a comparable control for the device group.

Patients depending on intravenous inotropic therapy have a dismal outcome and should be offered devices if eligible. However, the broader target for current mechanical circulatory support is the ambulatory heart failure population who are not yet dependent on inotropic therapy or continued hospitalization but have very limited functional capacity and poor prognosis for survival (profiles 4 to 6) (Table 1). In a recent survey, the majority of ambulatory patients with chronic symptomatic systolic heart failure indicated that they would consider an implanted device if they could walk less than a block or had <1 year to live (5). This has led to

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Table 1 INTERMACS Profiles of Limitation at Time of Implant

Profile	Description	Time Frame for Definitive Intervention
1	Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion with increasing lactate levels and/or systemic acidosis. "*Crash and burn*"	Needed within hours
2	Patient with declining function despite intravenous inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance. "*Sliding on inotropes*"	Needed within few days
3	Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support, but demonstrating repeated failure to wean owing to recurrent symptomatic hypotension or renal dysfunction. "*Dependent stability*"	Elective over a few weeks
4	Patient can be stabilized close to normal volume status but experiences frequent relapses into fluid retention, generally with high diuretic doses. Symptoms are recurrent rather than refractory. More intensive management strategies should be considered, which in some cases reveal poor compliance. "*Frequent flyer*"	Elective over weeks to months as long as treatment of episodes restores stable baseline, including nutrition
5	Patient is living predominantly within the house, performing activities of daily living and walking from room to room with some difficulty. Patient is comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. *"Housebound"*	Variable, depends upon nutrition, organ function, and activity
6	Patient without evidence of fluid overload is comfortable at rest and with activities of daily living and minor activities outside the home, but fatigues after the first minutes of any meaningful activity. *"Walking wounded"*	Variable, depends upon nutrition, organ function, and activity
7	A placeholder for future specification, patients without recent unstable fluid balance, living comfortably with meaningful activity limited to mild exertion.	Transplantation or circulatory support not currently indicated

Modified from Stevenson (9).

the consideration of "1 block or 1 year" as the signpost for referral for mechanical circulatory support.

Although a 1-block limitation is easy to identify, there has not been enough focus on how to predict 1-year mortality in advanced ambulatory heart failure. The last 20 years of trials in mild to moderate heart failure have allowed risk stratification before end-stage disease, as in the Toronto model and the Seattle Heart Failure Model (6,7). Such models need to better distinguish factors of heart disease severity that would be addressed by mechanical support from comorbidities such as renal function that also increase risk with device surgery. The impact of age is likely to remain profound, as in the REMATCH trial; for patients under 60 years, the 1-year survivals were 74% with device and 33% without, whereas they were 47% and 15% for older patients (1). More recent data at discharge from hospitalization for advanced heart failure led to the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) discharge risk score (8), which includes systolic blood pressure, blood urea nitrogen, serum sodium, beta-blocker use, 6-min walk, B-type natriuretic peptide, recent need for resuscitation, and loop diuretic dose. Prospective multicenter validation of risk scores specifically for late-stage heart failure is crucial to provide benchmarks past which to advance the field. Once equipoise has shifted toward devices, such benchmarks should replace the regulatory requirement for randomization back to medical therapy that has failed. To remain valid, however, device benchmarks have to keep up with contemporary therapy to reflect parallel downshifting risks (9).

It is assumed that patients portraying the more favorable INTERMACS profiles will have better outcomes with mechanical support than the earlier experiences of sicker patients. This seems reasonable, because a substantial mortality occurs in the perioperative period. It is not yet certain, however, that patients with less imminent compromise will derive greater net benefit with current devices. In the REMATCH trial, the 1-year survival of 57% with mechanical support for patients not initially on inotropic therapy was higher than for the overall population, but the medical survival was also higher at 49% (4).

Future Flight Plans

The concept of mechanical circulatory devices to support functional survival has been validated during the past 40 years of development and is further supported by the INTrEPID trial (3). Before the conclusion of this trial, it became clear from other experience that devices can no longer be tested in this dying population in a simple randomized trial design. However, the major questions remain simple: How long and how well do the patients live?

The answer to how long is currently expressed not by relative reductions of mortality, but in absolute survival with a given device. When survival without devices is negligible, the main component of the equation of net benefit is the survival with devices. A case could be made, particularly

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with hindsight, that the INTrEPID trial did not need a control group, because the major issue was outcome with the device, not outcome without it. Had 75% of patients survived 1 year, the trial would have been positive. Had 50% of patients survived 1 year, the device used would have been accepted as similar to the REMATCH device. Choices between the 2 would then be made by considering issues such as device durability and the risk of permanent neurologic events, both of which were high with the present device. However, the actual outcome of 25% survival at 1 year would not generate sufficient enthusiasm for implantation of this device even if it edged in front of the natural history of the disease.

For those patients who survive, the question is how well. In parallel with the equation for survival benefit, when quality of life is dismal the major component of quality benefit is the quality of life with the device. New York Heart Association functional class is too subjective to enlighten decision making. The heart failure questionnaires in the present study confirm that heart failure symptoms are markedly reduced, but different discomforts and limitations arising from the device also need to be captured. Average peak oxygen consumptions or 6-min walk distances, which are routinely collected in the INTERMACS registry, enhance understanding of the physiology of the supported circulation but do not facilitate individual decision making. An example of the type of data important to patients and their physicians was provided by the REMATCH trial, in which 67% of survivors on devices experienced no limitation in climbing a flight of stairs or walking 1 block, whereas 61% experienced some limitation bathing or dressing. The distribution of these individual responses will become increasingly important to guide timing of consideration for mechanical devices in the ambulatory population.

The pulsatile devices tested in the REMATCH and INTrEPID trials have successfully launched the clinical era for mechanical circulatory support. Experience is accumulating with the nonpulsatile pumps, which currently offer greater comfort and mobility with less circulatory pulsatility and reserve. The length of the flights for all has increased from a few months to a longer duration of durable support. The field will hopefully grow to a stage where controlled trials for advanced heart failure will have as their primary end points the functional and quality parameters, with assumed survival relegated to secondary end points of safety.

Whether devices are intended to bridge to transplant or to provide permanent support at the time of insertion has become less relevant, as many anticipated transplant candidates now wait a year or longer on mechanical support, during which they may become ineligible. Patients initially ineligible may improve on support to resolve contraindications and become eligible. Initial transplant eligibility should no longer segregate the durable devices or the recipients, 40% of whom currently cannot be categorized definitively as either bridge or destination at the time of implant. When outcomes are consistently good beyond 2 years, the devices will be seen not only as a bridge but as a feasible alternative to transplantation for the estimated 80,000 to 150,000 patients in the U.S. who could derive improved quality and length of life from cardiac transplantation if there were more than 2,200 hearts annually.

Initial reports from the INTERMACS registry indicate that almost 80% of devices currently implanted are for patients in INTERMACS profiles 1 and 2 (Drs. David Naftel and James Kirklin, personal communication, April 2, 2007). Current outcomes already warrant extension beyond these inotrope-dependent patients to profiles 4, 5, and possibly 6 (10). When device and patient lifespan extend beyond 3 years to 5 years, the field can lengthen to encompass patients whose disease is too early even to contemplate transplantation. Different devices than those currently used for complete circulatory support may eventually be used to prevent disease progression. At this horizon, design may once again become feasible for a traditional randomized control trial of device versus medical therapy, which will also have evolved by that time.

Progress in the field of mechanical circulatory support also has been held back by nonuniform collection of data by individual sites, companies, and countries. For a new technology with such promise for a disease with such prevalence, data consolidation must accelerate. A major advance is the formation of the INTERMACS registry, sponsored by the U.S. National Heart, Lung and Blood Institute (NHLBI). The INTERMACS registry has brought together the Food and Drug Association, Joint Commission on Accreditation of Healthcare Organizations, and Centers for Medicare and Medicaid Services in the U.S. to integrate and standardize the regulatory, certification, and post-market approval aspects with the surgical, cardiology, and nursing staff of expert centers. One area in which such standardization is critical is in the uniform definitions of adverse events, such as the neurologic events which occurred in most patients in the present trial. The pilot for this registry was launched by the International Society for Heart and Lung Transplantation (ISHLT), which is sponsoring the critical linking of the U.S. effort with the key international sites where many of the advances have been pioneered in Europe, Japan, the United Kingdom, and Australia. After the launch of this registry in July 2006, virtually all of the major U.S. centers are now enrolling patients, and the first formal analysis will be available in late spring 2007.

There is widespread consensus, including from task forces on mechanical circulatory devices from NHLBI and from ISHLT, that the next stage of acceleration will require the formation of a parallel advanced registry for patients with advanced heart failure. The INTrEPID trial demonstrates very clearly the dilemma posed when the target population has not been well characterized. Heart failure has a worse prognosis than most cancer, but heart failure lags far behind cancer in the robust staging of patient profiles and prognosis, as has been emphasized by Dr. Mariell Jessup. We need to move beyond the retrospective construction of risk scores

from mild to moderate heart failure populations and look ahead to how to stratify contemporary patients in real time. This registration of advanced heart failure is an essential part of the future flight plan, not only to launch the fledgling field of mechanical circulatory support, but also to provide each patient with the best among all the therapies becoming available.

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